How Sensitive Are Epidermal Growth Factor Receptor–Tyrosine Kinase Inhibitors for Squamous Cell Carcinoma of the Lung Harboring *EGFR* Gene–Sensitive Mutations?

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Introduction: Epidermal growth factor receptor *(EGFR)* mutations are found mostly in adenocarcinoma, and rarely in squamous cell carcinoma (SQC). Little is known about SQC harboring *EGFR* mutations.

Methods: Between April 2006 and October 2010, we investigated the incidence of *EGFR* activating mutations in SQC of the lung using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method. The efficacy of EGFR-tyrosine kinase inhibitors (TKIs) was retrospectively evaluated in patients with *EGFR*-mutated SQC. Further pathologic analyses were performed using immunohistochemistry.

Results: Thirty-three of 249 patients with SQC (13.3%) had *EGFR* mutations, including exon 19 deletion (19 of 33 patients, 58%), L858R point mutation in exon 21 (12 of 33, 36%), and G719S point mutation in exon 18 (2 of 33, 6%). Twenty of these 33 patients received EGFR-TKI therapy, and five of these 20 responded to EGFR-TKIs with a response rate of 25.0% (95% confidence interval [CI], 8.7%–49.1%). The patients' median progression-free survival and median overall survival were 1.4 months (95% CI, 0.7–5.8 months) and 14.6 months (95% CI, 2.9–undeterminable months), respectively. Approximately one third of the *EGFR*-mutated SQC patients achieved progression-free survival for longer than 6 months. Some of these patients had high carcinoembryonic antigen levels or a history of never smoking, or were positive for thyroid transcription factor-1.

Conclusions: Although EGFR-TKIs seem to be generally less effective in *EGFR*-mutated SQC than in *EGFR*-mutated adenocarcinoma, some *EGFR*-mutated SQC patients can obtain clinical benefit from EGFR-TKIs. To better identify these patients, not only *EGFR* mutation status, but also clinical factors and pathologic findings should be taken into consideration.

Key Words: Squamous cell carcinoma, *EGFR* mutation, Epidermal growth factor–receptor tyrosine kinase inhibitor.

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The efficacy of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) (gefitinib and erlotinib) has been demonstrated in patients with *EGFR*-sensitive mutations in non–small-cell lung cancers.[1,2] In patients of east Asian ethnicity, *EGFR* mutations are found in adenocarcinoma (ADC) relatively frequently (30%–40%), but rarely in other histologic subtypes.[3] We occasionally detect *EGFR* mutations in squamous cell carcinoma (SQC) in our clinical practice. However, there is little data on the efficacy of EGFR-TKIs for SQC harboring *EGFR* mutations.

The purposes of the present study were: first, to investigate the incidence of *EGFR* mutations in SQC patients in Japanese populations using a highly sensitive polymerase chain reaction (PCR) method and to identify the characteristics of *EGFR*-mutated SQC patients, and second, to evaluate the efficacy of EGFR-TKIs in these patients. In addition, we compared the efficacy of EGFR-TKIs between *EGFR* mutation-positive and -negative SQC patients. We also performed immunohistochemistry (IHC) analyses to identify the pathologic features of histologic samples of *EGFR*-mutated SQC.

PATIENTS AND METHODS

Patients and Specimens

Between April 2006 and October 2010, an *EGFR* mutational analysis was performed in tumor specimens from 249 patients with SQC at our institutes, regardless of whether or not the patients had undergone EGFR-TKI therapy. Tumor specimens were obtained by various methods: ultrasound or computed tomography–-guided needle biopsy, bronchoscopic transbronchial biopsy, cell blocks of malignant effusion, and surgical tissues. We isolated tumor DNA from various specimens, and *EGFR* mutations were analyzed using the peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp method, as reported by Nagai et al.[4]

We investigated the incidence of *EGFR* mutation in SQC of the lung. Patients with *EGFR*-mutated SQC were identified from records at our institutes, and their characteristics (age, sex, smoking history, and types of *EGFR* mutation) were examined. Patients who reported never having smoked in their lifetime were defined as neversmokers, those who had smoked within 1 year of diagnosis were categorized as current smokers, and the rest were considered former smokers. This study was approved by the Institutional Review Board, and informed consent regarding the *EGFR* mutational analysis was obtained from all patients.

Evaluation of EGFR-TKI Efficacy

The initial doses of gefitinib and erlotinib were 250 mg/day and 150 mg/day, respectively. Each drug was orally administered once a day until progressive disease (PD) or unacceptable toxicity was noted. Dose reduction or interruption was performed in the case of toxicity. Chest radiography was performed every 1 to 4 weeks and a chest computed tomography scan was performed every 1 to 3 months. These procedures were also performed as needed to confirm response and disease progression. Tumor response was retrospectively evaluated using the Response Evaluation Criteria in Solid Tumors.[5] Stable disease (SD) was defined as disease control maintained for at least 8 weeks. The duration of progression-free survival (PFS) was calculated from the date of initiation of EGFR-TKIs to the date of disease progression. Overall survival (OS) time was determined from the date of initiation of EGFR-TKIs to the date of death.

IHC Analyses and Pathologic Features

We retrospectively performed IHC analyses of 29 available histologic samples from the 33 patients harboring *EGFR* mutations to examine their pathologic characteristics in greater detail. Representative formalin-fixed paraffin-embedded tumor blocks were selected and used for the IHC. After deparaffinization of 3- to 4-μm-thick sections, heat-induced antigen retrieval was performed with an ethylenediaminetetraacetic acid solution (pH 8.0). The sections were treated with 3% hydrogen peroxide to block endogenous peroxidase activity. The reaction of relevant antibodies was carried out following the manufacturer's instructions.

We adopted a multiplex IHC analysis with four kinds of antibody cocktail (ADC cocktail and SQC cocktail, Pathology Institute Corp., Toyama, Japan), consisting of the following monoclonal antibodies: mouse for thyroid transcription factor 1(TTF-1; clone SPT24), mouse for napsin-A (clone TMU-Ad02), mouse for p63 (clone 4A4), and mouse for CK14 (clone LL002). TTF-1/napsin-A for the differentiation of ADC and p63/CK14 for SQC have been reported as effective IHC antibodies.[6–11] In this multiplex IHC method, TTF-1 labels ADCs' nuclei, and napsin-A labels cytoplasm. SQC carcinomas could be differentiated from ADCs by the following staining patterns: nuclear staining with p63 and cytoplasmic staining with CK14. Expert pathologists (KN and YI) evaluated the immunoreactivities. We defined tumors exhibiting a diffuse staining pattern or at least a mean positive area of 10% or more in the relevant cells as immunopositive (+); tumors exhibiting weak or 10% or lesser focal staining patterns as slightly positive (±); and tumors whose staining was completely absent as negative (−). The efficacy of a similar method using the same four antibodies has been described.[12] We also pathologically reassessed these 29 histologic samples to examine tumor differentiation and SQC features such as keratinization.

STATISTICAL ANALYSIS

The response rate (RR) and disease-control rate were compared between the *EGFR*-mutation–positive and –negative patients using Fisher's exact test. PFS and OS curves were estimated according to the Kaplan–Meier method. PFS and OS were compared between the *EGFR*-mutation–positive and –negative patients using the log-rank test. Statistical analysis was performed using JMP 7 (SAS Institute, Inc., Cary, NC).

RESULTS

Incidence of *EGFR* Mutations in SQC of the Lung

With the PNA-LNA PCR clamp method, *EGFR* mutations were detected in 33 of the 249 patients with SQC of the lung, making the incidence of *EGFR* mutations in these SQCs 13.3%.

Characteristics of *EGFR*-Mutated SQC Patients

The characteristics of the patients harboring *EGFR* mutations are shown in Table 1. Twelve of the 33 patients (36%) were women, and seven (21%) were neversmokers. Two (6%) patients had a point mutation in exon 18 (G719X), 19 (58%) had a deletion mutation in exon 19, and 12 (36%) had a point mutation in exon 21 (L858R).

Efficacy of EGFR-TKIs

Between January 2000 and October 2010, 81 patients with SQC received gefitinib or erlotinib as their first TKI therapy (excluding readministration of EGFR-TKIs). All these patients had unresectable and advanced/metastatic disease. Of these 81 patients, 20 were *EGFR*-mutation positive, 33 were *EGFR*-mutation negative, and 28 were unknown. EGFR-TKIs were administered to 20 of the 33 SQC patients harboring *EGFR* mutations, and to the 33 *EGFR*-mutation–negative patients. A comparison of characteristics

TABLE 1. Characteristics of Patients with *EGFR*-Mutated Squamous Cell Carcinoma (n = 33)

Patient Characteristics	No. of patients	%
Age (yr)		
Median (range)	70 (49–83)	
Sex		
Male	21	64
Female	12	36
Smoking history		
Never	7	21
Former	13	39
Current	13	39
Types of *EGFR* mutation		
Exon 18 (G719X)	2	6
Exon 19 (deletion)	19	58
Exon 21 (L858R)	12	36

EGFR, epidermal growth factor receptor.

between the *EGFR*-mutation–positive and –negative patients is shown in Table 2. Most of the *EGFR*-mutation–positive patients received gefitinib, whereas most of the *EGFR*-mutation–negative patients received erlotinib. Other patient characteristics, including previous and subsequent therapies, were not significantly different between the *EGFR*-mutation–positive and –negative patients.

Among the *EGFR*-mutation–positive patients (n = 20), one complete response (CR), four partial response (PR), and six SD were confirmed, seven patients were judged as having PD, and the responses of two patients were not evaluable. Among the *EGFR*-mutation–negative patients (n = 33), zero CR, three PR, 11 SD, 18 PD, and one not evaluable were confirmed. The RRs (*EGFR*-positive versus -negative) were 25.0% (95% confidence interval [CI], 8.7%–49.1%) versus 9.1% (95% CI, 1.9%–24.3%), respectively (p = 0.1372). The disease-control rates were 50.0% (95% CI, 31.5%–76.9%) versus 42.4% (95% CI, 25.5%–60.8%), respectively (p = 0.7765).

The median PFS values (*EGFR*-positive versus -negative) were 1.4 months (95% CI, 0.7–5.8 months) versus 1.8 months (95% CI, 1.0–2.4 months) (p = 0.1734) (Fig. 1). Approximately one third of the 20 *EGFR*-mutation–positive patients obtained a PFS longer than 6 months. The median OS values were 14.6 months (95% CI, 2.9–undeterminable months) versus 11.0 months (95% CI, 5.7–15.7 months) for the *EGFR*-mutation–positive and –negative patients, respectively (p = 0.5472) (Fig. 2).

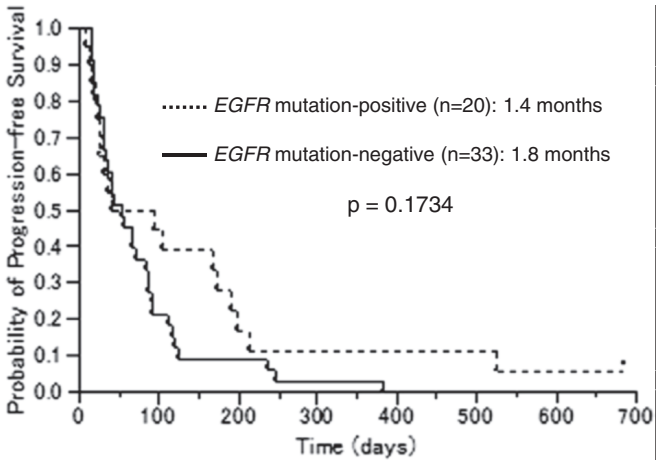
IHC Results and Pathologic Features

The results of the IHC analyses performed on the 29 available histologic samples from 33 *EGFR*-mutated SQC patients are shown in Table 3. Clinical, mutational, and pathologic characteristics are also shown. Thirteen (45%) poorly, nine (31%) moderately, and seven (24%) well-differentiated SQCs were diagnosed. Elevated carcinoembryonic antigen (CEA) levels (>10 ng/ml) were confirmed in

TABLE 2. Comparison of *EGFR*-Mutation–Positive and –Negative Squamous Cell Carcinoma Patients

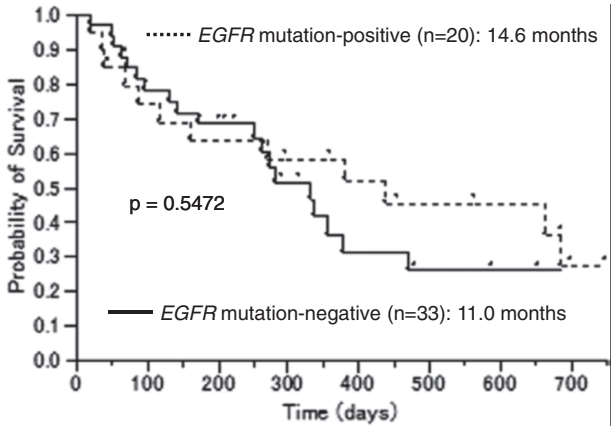
Characteristics	*EGFR* Mutation -Positive (n = 20)	*EGFR* Mutation -Negative (n = 33)
Age (yr)		
Median (range)	68 (56–82)	67 (44–84)
Prior regimens		
Median (range)	2 (0–4)	3 (2–6)
Sex		
Male	14 (70%)	26 (79%)
Female	6 (30%)	7 (21%)
Smoking history		
Never	4 (20%)	3 (9%)
Former	6 (30%)	10 (30%)
Current	10 (50%)	20 (61%)
PS (ECOG)		
0, 1	18 (90%)	28 (85%)
2, 3, 4	2 (10%)	5 (15%)
Types of EGFR-TKI		
Gefitinib	18 (90%)	1 (3%)
Erlotinib	2 (10%)	32 (97%)
Front-line therapy		
Platinum doublets	14 (70%)	23 (70%)
Nonplatinum doublets	1 (5%)	3 (9%)
Monotherapy	2 (10%)	7 (21%)
Gefitinib	3 (15%)	0 (0%)
Subsequent therapies		
Cytotoxic therapies	16 (80%)	29 (88%)
None	4 (20%)	4 (12%)

PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.



EGFR, epidermal growth factor receptor.

FIGURE 1. Progression-free survival of *EGFR*-positive versus -negative squamous cell carcinoma patients. *EGFR*-mutation positive (n = 20): 1.4 months; *EGFR*-mutation negative (n = 33): 1.8 months. p = 0.1734



EGFR, epidermal growth factor receptor.

FIGURE 2. Overall survival curves of *EGFR*-positive and -negative squamous cell carcinoma patients. *EGFR* mutation-negative (n = 33): 11.0 months; *EGFR* mutation-positive | (n = 20): 14.6 months. p = 0.5472.

nine patients. Keratinization was found in 21 (72%) of the 29 samples. With respect to IHC results for SQC, p63 and CK14 were positive in 25 (86%) and 12 (41%) patients, respectively, whereas IHC results for ADC, TTF-1, and napsin-A were positive in six (21%) and four (14%) patients, respectively.

DISCUSSION

Recent reports document the incidence of *EGFR* mutations in SQC of the lung as extremely rare: 2.6%[3] (6 of 230; includes adenosquamous and large-cell carcinoma), 0% (0 of 454),[13] and 0% (0 of 102).[14] The incidence in the present study was 13.3% (33 of 249), much higher than those of the cited studies. We used the PNA-LNA PCR clamp method, which is a highly sensitive PCR technique, so that minor *EGFR*-mutated populations in an SQC tumor might be detected. Similarly, Tanaka et al.[15] demonstrated that the incidence of *EGFR* mutations in non-ADC including SQC was 12.1% (8 of 66) using the same method. Moreover, using an even more

TABLE 3. Clinical, Mutational, and Pathologic Factors, and Immunohistochemistry Findings

No.	Age(yr) Sex	CEA ng/ml	Smoking Status	*EGFR* Mutation	Response to TKIs	Differentiation/ Keratinization	p63/CK14	TTF-1/ Napsin-A
1	64F	270	Never	Del-19	CR	Poor/−	− /−	+/−
2	56M	1.5	Current	Del-19	PR	Poor/−	− /−	− /−
3	68F	14.3	Former	Del-19	SD	Moderate/+	+/−	− /−
4	78F	2.6	Former	Del-19	/	Moderate/+	+/+	− /−
5	62M	3.8	Current	Del-19	PD	Moderate/+	+/−	+/−
6	74M	3.1	Former	L858R	/	Moderate/+	+/+	− /−
7	78M	2.2	Former	L858R	/	Well/+	+ / +	− /−
8	56M	7.2	Former	Del-19	PR	Poor/+	+/−	− /−
9	59M	51.9	Former	L858R	SD	Moderate/+	+/−	±/+
10	73M	4.1	Current	Del-19	/	Well/+	+ / +	− /−
11	60M	16.5	Former	Del-19	/	Well/+	+/−	− /−
12	56M	4.3	Former	L858R	/	Moderate/+	+/−	− /−
13	81F	7.3	Never	G719A	/	Poor/+	+/−	− /−
14	74M	19.3	Former	G719S	/	Moderate/+	+/+	+/+
15	68M	8.3	Current	Del-19	SD	Poor/+	+ / ±	− /−
16	67F	0.9	Never	Del-19	SD	Well/+	+/+	− /−
17	49M	1.1	Current	L858R	/	Moderate/+	+/−	− /−
18	73M	3.5	Former	L858R	SD	Poor/−	+/−	− /−
19	75F	499	Never	L858R	PR	Poor/−	+/−	+/+
20	60M	4.8	Current	Del-19	NE	Well/+	+/+	− /−
21	77M	6.1	Current	L858R	PD	Poor/−	+/+	− /−
22	75M	4.1	Current	Del-19	PD	Well/+	−/+	− /−
23	83M	/	Current	L858R	/	Poor/−	+/−	− /−
24	76M	4.8	Former	Del-19	NE	Moderate/+	+/−	− /−
25	54F	/	Current	L858R	/	Poor/+	+/+	− /−
26	67F	22.1	Current	L858R	PD	Poor/−	+/−	− /−
27	68M	/	Current	Del-19	/	Poor/−	− /−	− /−
28	82F	266	Never	L858R	SD	Well/+	+/+	+/+
29	74M	14.0	Former	Del-19	PD	Poor/+	+/−	− /−

CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CK, cytokeratin; TTF-1, thyroid transcription factor-1; Del-19, deletion mutation in exon 19; L858R, point mutation in exon 21; G719X; point mutation in exon 18; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

sensitive technique (denaturing high-performance liquid chromatography) that can detect *EGFR* mutations even in plasma DNA samples, Bai et al.[16] demonstrated that the incidence of *EGFR* mutations in non-ADC including SQC was 20.3% (12 of 59). These higher incidences were all reported from Asia, and previous reports from western countries reveal that *EGFR* mutations are rarely found in white SQC populations. Our present findings and the results of the Tanaka et al. and Bai et al. studies reveal a higher incidence of *EGFR* mutations in SQC among Asian populations compared with that in white populations, after using highly sensitive methods. The mutation rate of SQC may vary by methodology and ethnicity, as does that of ADC.

The characteristics of the *EGFR*-mutated SQC patients in the present study show that more women (36%) and neversmokers (22%) were included than are typical among SQC patients. The lack of smoking history is unusual for typical SQC (1%–3% in other studies).[17–19] This implies that *EGFR*-mutated SQC may have a different nature from typical SQC. The proportions of each *EGFR* mutation in our study (G719X, 6%; del-19, 58%; and L858R, 36%) were mostly consistent with those previously reported.[20] If uncommon mutations are frequently detected, we need to address the possibility of experimental artifacts. Marchetti et al.[21] pointed out that experimental artifacts because of postmortem deamination are possible in cases of uncommon *EGFR* mutations, especially if the samples are extracted from paraffin-embedded small samples. Our data included no uncommon mutations. To the best of our knowledge, there are no reports that common mutations such as del-19, L858R, and G719X arise as artifacts. We therefore believe that it is unlikely that our data include experimental artifacts.

In the present study, the RR and median PFS of the *EGFR*-mutated SQC patients were 25.0% and 1.4 months, respectively. Shukuya et al.[22] also conducted a pooled analysis of 27 published *EGFR*-mutated SQCs, and they found that the RR and median PFS were 30% and 3.1 months, respectively. These results are clearly inferior to pivotal data for *EGFR*-mutated ADC, for which, in general, the RR and median PFS have been reported to be 70% to 80% and 9 to 11 months, respectively.[23–27] EGFR-TKIs seem to be less effective in *EGFR*-mutated SQC than in *EGFR*-mutated ADC.

However, Figure 1 shows that approximately one third of the *EGFR* mutation-positive patients obtained a PFS of longer than 6 months. In addition, Figure 2 shows that after approximately 1 year, survival curves separate between the *EGFR* mutation-positive and -negative patients, a result which may be because of the efficacy of EGFR-TKIs. We think it important to be able to identify from all *EGFR*-mutated SQC patients those who can obtain clinical benefit from EGFR-TKIs.

Among the *EGFR*-mutated SQC patients treated with EGFR-TKIs, four (80%) of the five TTF-1–positive patients obtained clinical benefit (CR, PR, or SD). Patients with TTF-1–positive tumors were likely to have ADC propensity. Meanwhile, only one (9%) of the 11 p63/CK14-positive and TTF-1/napsin-A-negative tumors responded to EGFR-TKIs. Tumors with these IHC patterns were more compatible with pure SQC lineages. Further, three (75%) of the four patients with both p63/CK14- and TTF-1/napsin-A–positive tumors obtained clinical benefit. These double-positive IHC patterns suggest mixed components of ADC and SQC. Patient 2 was the only patient with both p63/CK14- and TTF-1/napsin-A–negative tumors, and he responded to gefitinib. The TTF-1/p63 double-negative profile is interpreted as indeterminate but favoring ADC.[28] Considering these results, patients with tumors containing greater ADC lineages can obtain more clinical benefit from EGFR-TKIs. Conversely, patients with pure SQC tumor lineages may obtain little clinical benefit.

Of the group of patients who obtained clinical benefit from EGFR-TKIs, some were neversmokers and/or exhibited high CEA levels. Patient 1 was a nonsmoking woman with markedly elevated CEA. Her initial diagnosis was poorly differentiated SQC. It is well known that poorly differentiated ADC and SQC can seem indistinguishable by light microscopy.[29] In fact, the IHC pattern of Patient 1 suggested ADC lineages. We consider her tumor to be poorly differentiated ADC, morphologically mimicking SQC. Patients 9, 19, and 28 were light smokers, and their CEA levels were also elevated. In Patient 9, apparent keratinization was confirmed at the initial pathologic examination. However, after staining with TTF-1, glandular patterns emerged in the retrospective pathologic reassessment. IHC showing a p63/CK14 and TTF-1/napsin-A double-positive pattern suggests mixed components of ADC and SQC. Although the definition of AD-SQC requires that both glandular and squamous components represent at least 10% of the tumor mass,[30] the double-positive IHC pattern represents the AD-SQC lineage. The incidence of *EGFR* mutations in AD-SQC is known to be similar to that in ADC, and their responsiveness to EGFR-TKIs has also been reported.[31–36] We speculate that some *EGFR*-mutated SQCs (especially those that obtain clinical benefit from EGFR-TKIs) are indeed an incomplete sampling of AD-SQC and poorly differentiated ADC morphologically mimicking SQC. To identify these patients, it is important to examine not only IHC results, but also clinical characteristics such as smoking status and CEA level.

Approximately one half of the *EGFR*-mutated SQC patients failed to benefit from EGFR-TKIs in the present study. The absence of *EGFR* mutations has been demonstrated in pure SQC,[28] and we also consider *EGFR*-mutated SQC not to be pure SQC. In our speculation, a highly sensitive PCR technique can detect *EGFR*-mutated, malignant (probably ADC) cells as a minor population in a tumor, but SQC cells as a major population are wild-type *EGFR*. Thus, EGFR-TKIs for *EGFR*-mutated SQC are generally less effective than in *EGFR*-mutated ADC. A minor glandular component may not be represented in microscopically scrutinized tissue.

Notably, similar situations have been reported in small-cell lung cancer (SCLC).[37–41] These reports suggest that *EGFR* mutations are rare, but can be found in SCLC, and that EGFR-TKIs are generally less effective in *EGFR*-mutated SCLC than in *EGFR*-mutated ADC, even though some *EGFR*-mutated SCLC patients obtained clinical benefit from EGFR-TKIs. Most of these patients were neversmokers, and had a mixed ADC histology. Regardless of SQC and SCLC histologies, the sensitivity of EGFR-TKIs in patients with non-ADC harboring *EGFR* mutations may depend on the proportion of *EGFR*-mutated ADC components in the whole tumor.

Some of our *EGFR*-mutated SQC patients were diagnosed by small specimens that might have included an incomplete sampling of AD-SQC. Roggli et al.[42] addressed histologic heterogeneity in a comprehensive study of 100 lung cancer cases in which two (5%) of 39 ADC patients showed an SQC component, and an ADC component was found in four (15%) of 27 SQC cases (15%). In these cases, the morphologic features of SQC or ADC differentiation were focal or not distinguishable. Pathology experts have noted the difficulty and complexity of pathologic diagnosis, especially based on small biopsies.[29]

The diagnostic limitations of small biopsies and intratumoral heterogeneity make definitive diagnoses difficult. Clinicians should understand the limitations of pathologic diagnosis based on small biopsies, and they need to cooperate with pathologists to better reach a diagnosis for individual patients. It has recently become more important to distinguish SQC from ADC to decrease the incidence of life-threatening hemorrhage with bevacizumab,[43] to obtain better efficacy with pemetrexed,[44] and to select populations harboring the more frequent *EGFR* mutations.[3]

In conclusion, the incidence of *EGFR* mutations in SQC of the lung was not low in the Japanese populations tested with the present highly sensitive PCR method. Although the efficacy of EGFR-TKIs for *EGFR*-mutated SQC is generally inferior to that for *EGFR*-mutated ADC, some *EGFR*-mutated SQC patients can obtain clinical benefit from EGFR-TKIs. In the Japanese population (which has a high incidence of *EGFR* mutations), *EGFR* mutational analysis is recommended even for SQC to identify the patients who might benefit, and other factors should also be taken into consideration, including clinical factors such as smoking status and pathologic findings such as differentiation and IHC results, and tumor markers, such as CEA level. Considering the utility and complexity of pathologic diagnoses, interaction between clinicians and pathologists has become more important. Given that the present data are retrospective and that we had a small sample size, RR and PFS are very soft endpoints, and the RR and PFS were assessed by the investigators. In addition, the interval for the restaging imaging was highly variable, and this represents a bias for PFS assessment. Further investigations are warranted to validate the efficacy of EGFR-TKIs for *EGFR*-mutated SQC patients. We are therefore conducting a phase II trial to evaluate the efficacy of gefitinib for *EGFR*-mutated non-ADC NSCLC.

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